REMARKS

This reply is intended to distinctly and specifically point out presumed errors in the Examiner's Action, to respond to every ground of objection and rejection, and to advance this case to allowance.

Claim 1 has been amended to specify N-[4-chloro-2-hydroxy-3-(4-methyl-piperazine -1-sulfonyl)-phenyl]-N'-(2-chloro-3-fluorophenyl) urea or a pharmaceutically acceptable salt thereof. No new matter is added.

Claim 3 has been added to specify three pulmonary diseases: asthma, chronic obstructive pulmonary disease and adult respiratory distress syndrome. No new matter is added.

Claim 4 has been cancelled.

New claim 5, dependent on amended claim 3, has been added to specify chronic obstructive pulmonary disease. No new matter is added.

I. Rejections under 35 U.S.C. § 112

The Examiner has rejected claim 3 under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. According to the Examiner, claim 3 is of indeterminate scope because it defines diseases by their underlying cause, and the claim language of claim 3 may read on diseases not yet known. Additionally, the Examiner asserts that determination of a given disease based on whether or not it responds to a mode of action (IL-8 receptor binding) involves much experimentation. The Examiner asserts that the test for determining compliance with 35 U.S.C. § 112, second paragraph, is whether Applicants have clearly defined their invention, not what may be discovered by future research.

Applicants respectfully traverse the present rejection, especially in light of the present amendment limiting the diseases in claim 3 to three pulmonary diseases: asthma, chronic obstructive pulmonary disease and adult respiratory distress syndrome. Amended claim 3 does not contain diseases defined by their underlying cause or read on diseases not yet known. No undue experimentation is required to determine whether the three pulmonary diseases listed would respond to a given mode of action. The invention is clearly defined and the present rejection should be withdrawn.

The Examiner has also rejected claims 3 and 4 under 35 U.S.C § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserts that the claims

contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

According to the Examiner, the scope of the diseases claimed is not enabled based on the instant compounds' ability to selectively antagonize IL-8 receptors in the *in vitro* assays described in the specification. Further, according to the Examiner, the references cited in the specification do not indicate that there are any known IL-8 antagonists for any one use, much less the scope provided.

The Examiner asserts that, because the utility is unusual or difficult to treat or speculative, she has the authority to require evidence that tests relied upon are reasonably predictive of *in vivo* efficacy. The Examiner requires that any evidence relied on must clearly show a reasonable expectation of success *in vivo* for any additional diseases that may still be embraced in response to the office action, considering the factors of breadth of claims, level of skill in the art, state of the prior art, direction or guidance and working examples.

Applicants respectfully traverse the Examiner's rejection, especially in light of the present amendment which limits claim 3 to three pulmonary diseases, and cancels claim 4. One skilled in the art has ample enablement to make and/or use the present invention to treat the three specified pulmonary diseases: asthma, chronic obstructive pulmonary disease and adult respiratory distress syndrome.

Applicants provide the Examiner with Hay, *et al.,* Interleukin-8 receptor antagonists in pulmonary diseases, Current Opinion in Pharmacology, 2001, **1**:242-247 ("Hay *et al.*"). Hay et al., discloses that IL-8 and related chemokines are found at elevated levels in the lungs of patients with different pulmonary diseases. Hay et al., thus concludes that there exists "considerable evidence to suggest that the recruitment and activation of inflammatory cells in the lung contributes significantly to the pathophysiology of pulmonary diseases" (p. 246, col. 1). Pulmonary diseases disclosed in Hay et al., include asthma (p. 244, col. 2), chronic obstructive pulmonary disease (p. 243, col. 1) and acute respiratory distress syndrome (p. 244, col. 2). Hay et al., further reports that specific IL-8 receptor antagonist molecules have been tested for pulmonary uses.

Applicants therefore assert that the diseases claimed in amended claim 3 are enabled. The diseases are specified, the utility is not speculative and the tests relied upon are reasonably predictive of *in vivo* efficacy. One skilled in the art would have a reasonable expectation of success given that three pulmonary diseases are claimed and that the prior art has disclosed

the present uses for IL-8 receptor antagonists. Contrary to the assertions of the Examiner, the level of skill in the present art is not low, as evidenced by Hay, *et al*. Applicants respectfully request that the present rejection be withdrawn.

II. Rejection under 35 U.S.C. § 103 (a)

The Examiner has rejected claims 1-4 under 35 U.S.C. §103 (a) as being unpatentable over Jin (WO '442). According to the Examiner, Jin describes similar compounds having the same mechanism of action from which various uses are asserted included those claimed herein. The Examiner states that the piperazino species on p. 10, lines 20 – 21 of Jin differs from the present compound only in the presence of 2 chlorines on the phenyl ring instead of the present 2-chloro-3-fluorophenyl derivative. Further, the Examiner states that all halos are taught as suitable substituents on the phenyl ring as can be seen from the definition of Y on page 4. Thus, the Examiner concludes that it would have been obvious to one skilled in the art at the time of the instant invention to replace either chloro with fluorine, resulting in the present compound: N-[4-chloro-2-hydroxy-3-(4-methyl-piperazine -1-sulfonyl)-phenyl]-N'-(2-chloro-3-fluorophenyl) urea, or a pharmaceutically acceptable salt thereof.

Applicants respectfully traverse the present rejection and assert that the PTO has not met its burden of establishing a *prima facie* case of obviousness. For the burden to be met, a reference must both suggest doing what is contemplated by the present invention and provide a skilled artisan with sufficient basis for a reasonable expectation of success.

The reference quoted by the Examiner would not motivate one skilled in the art to select the variables to arrive at the present compound. Undue experimentation would be involved to extrapolate from the reference cited to the present compound. Numerous attempts at variation would have to be made to arrive at the compound claimed.

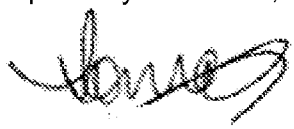
While Jin does disclose a piperazino species with two chlorines on the phenyl ring instead of the present 2-chloro-3-fluorophenyl derivative, this species is one of over 150 other compounds also disclosed. Jin broadly teaches dihydroxy diphenyl urea derivatives, with multiple variations possible at each of its values of R_b, $(R_1)_m$, Y and n. The Y values on page 4 of the specification include, in addition to the halogen value cited by the Examiner, numerous other possible values on the phenyl ring. The selection of the particular fluoride substitution at the particular position on the phenyl ring, in combination with the particular selections of the R_b, $(R_1)_m$, Y and n values that would result in N-[4-chloro-2-hydroxy-3-(4-methyl-piperazine -1-sulfonyl)-phenyl]-N'-(2-chloro-3-fluorophenyl) urea, or a pharmaceutically acceptable salt thereof, could only be made with the hindsight provided by the present application. The

Examiner has selected this particular combination of values from the wide range of alternatives provided by Jin even though there is no specific direction to this selection. Thus, in the present case, contrary to the assertions of the Examiner, a skilled artisan would not reasonably select the one compound presently claimed due to the genus taught by Jin, as millions of attempts at variation could be made before arriving at the desired result.

In conclusion, the PTO has not met its burden of establishing a *prima facie* case of obviousness because a skilled chemist would have no motivation to extrapolate to the present compound, or a salt thereof, given the cited reference. Applicants therefore respectfully request that the present rejection be withdrawn.

In view of the above remarks, reconsideration of this application is requested. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned agent at the number below.

Respectfully submitted,



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